UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,642	01/28/2004	Anthony Atala	105447-2	4621

21125 7590 12/23/2008

NUTTER MCCLENNEN & FISH LLP
WORLD TRADE CENTER WEST
155 SEAPORT BOULEVARD
BOSTON, MA 02210-2604

EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
12/23/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@nutter.com

Office Action Summary	Application No.	Applicant(s)	
	10/766,642	ATALA ET AL.	
	Examiner	Art Unit	
	ALLISON M. FORD	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2008 and 16 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-10,12,23-26,28,29 and 33-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-10,12,23-26,28,29 and 33-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/15/2008 has been entered. The supplemental amendment filed 12/16/2008 has also been received and entered. Claims 1, 23, 27 and 33-37 have been amended; claims 5, 11, 13-22 and 30-32 are cancelled. Claims 1-4, 6-12, 23-26, 28-29 and 33-37 remain pending in the instant application, all of which have been considered on the merits.

Response to Arguments/Amendments

Applicants' arguments submitted on 9/15/2008 have been fully considered.

In response to the rejection of claims under 35 USC 103(a) Applicants have argued that none of the cited references, alone or in combination, teach all of the features of the method of the instant claims. Applicant notes the differences between each reference and the method of the instant claims. Applicants further assert there is no suggestion that the primary reference, Naughton et al, is unsatisfactory, and thus there is no motivation to combine Naughton et al with any of the secondary references. Applicants further assert that Rinsch et al actually teaches away from use of encapsulated myoblasts transfected to express VEGF, as Rinsch et al do not report significant flap survival over controls (wherein flap survival may be correlated to angiogenesis).

Applicants' arguments have been fully considered, but are not found persuasive.

With regards to Applicant's argument that there is no suggestion or motivation to modify the method of primary reference Naughton et al because the method of Naughton et al is not shown to be unsatisfactory, it is respectfully submitted that such a requirement (recognition of a deficiency in the art and an explicit motivation to modify or combine prior art teachings) is not the standard for a proper rejection under 35 USC 103(a). In the Supreme Court decision in *KSR International Co v Teleflex Inc* the court stated, "Rigid application of "teaching, suggestion, or motivation" test, under which patent claim is proved obvious only if prior art, nature of problem addressed by inventor, or knowledge of person having ordinary skill in art reveals some motivation or suggestion to combine prior art teachings, is inconsistent with expansive and flexible "functional approach" to resolution of obviousness issue, under which scope and content of prior art are determined, differences between prior art and claims at issue are ascertained, level of ordinary skill in pertinent art is resolved, and secondary considerations such as commercial success, long felt but unsolved needs, and failure of others may be considered if doing so would prove instructive; rigid TSM approach is therefore rejected." See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) at page 1386 (emphasis added). In the instant case, the teachings of each of the cited references show that each element of the current claim was known in the art, yet no one reference taught all limitations in a single embodiment. The level of skill in the field of tissue engineering is high and thus one having ordinary skill in this art would have been capable of combining the known elements (therapies for treating of ischemic tissue and promoting angiogenesis therein) into a single therapeutic method for the same purpose as each individual therapy. When combining elements taught in several prior art references into a single method arrives at the instant invention, the final combination is likely not the product of innovation but of ordinary skill and common sense, especially in the absence of evidence showing unexpected results. See *Id.* at 1397.

With regards to Applicants' arguments that the cited references do not teach each and every limitation of the instant claims, and Rinsch et al actually teaches away from the instant invention, it is respectfully submitted that Applicants have only shown that the cited references, individually, do not teach all the limitations of the current claims (Penn et al does not teach encapsulation; Springer et al does not teach transient transfection), yet a reference merely not teaching every limitation does not constitute teaching away by that reference. See *In re Grasselli* 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983). None of the references were applied as anticipatory, but rather were relied upon in combination, as no one reference was submitted to disclose all of the claimed limitations. With regards to the Rinsch et al reference, while Applicants have submitted that Rinsch et al states the implantation of their encapsulated VEGF-transfected cells did not result in significant flap survival, this point is noted; however, it is respectfully submitted that Applicants are reading Rinsch et al too narrowly. A review of the full teachings of Rinsch et al shows that Rinsch et al did report that VEGF-transfected myoblasts did induce an invasive response in neighboring BME cells in the *in vitro* model (See Rinsch et al, Pg. 529, col. 1, first full paragraph), and that while the encapsulated VEGF-transfected cells did not have a significant effect on survival of skin flaps, a modest increase in the number of distally located small diameter blood vessels was observed near the implants (See Rinsch et al, Pg. 529, col. 1, second full paragraph). Furthermore, Rinsch et al go on to qualify the low results achieved with the VEGF-transfected cells, stating the failure of VEGF in their model may be due to a number of controllable factors, such as endothelial cell specificity, duration of the implantation period (period being shorter than necessary for optimal VEGF secretion by myoblasts), and level of VEGF administered (higher levels of VEGF may provide more therapeutic benefit) (See Rinsch et al, paragraph spanning col. 1-2 of Pg. 529). Therefore, while the actual results reported by Rinsch et al do not show significant angiogenic potential, the teachings of Rinsch et al at least show that 1) encapsulation of VEGF-transfected myoblasts was known in the art, and 2) implantation of encapsulated VEGF-transfected myoblasts has potential to induce

angiogenesis *in vivo*, thereby providing at least a suggestion to try. Therefore reliance on each of the secondary references, including Rinsch et al is maintained as appropriate.

In whole, neither the arguments, nor the amendments suffice to differentiate the claimed subject matter as patentably distinct over the prior art. The rejections of record stand.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-10, 12, 23-26, 28-29 and 33-37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al, (US 2003/0007954), in view of Atala (US Patent 6,479,064), MacLaughlin et al (US Patent 6,692,738), Springer et al (J Gene Med, 2000), Rinsch et al (Gene Therapy, 20001) and Penn et al (US 2004/0161412 A1, as fully supported by provisional applications 60/405274 & 60/424065).

At the time the invention was made the need for effective methods of reconstructing and repairing ischemic tissues was well recognized in the art (See, e.g. Naughton et al, page 1). It is the opinion of the Office that Applicants' currently claimed methods are a combination of several treatment methods which were each individually taught in the prior art. Absent a showing that the claimed combination of treatment methods produces unpredicted results, it is respectfully submitted that the combination of multiple treatment methods, each intended to reconstruct and repair ischemic tissue and to promote angiogenesis therein, would have been obvious to one of ordinary skill in the art at the time the invention

was made. It has been held that when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions (in the instant case the 'solutions' would be the treatment methods), a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. See *KSR International Co v Teleflex 82 USPQ2d 1385 (US 2007) at page 1397.*

Naughton et al disclose a method for repairing ischemic tissue, particularly ischemic myocardial tissue, involves implantation of tissue engineered stromal tissue adjacent to the ischemic tissue to promote new cellular growth and angiogenesis in the ischemic tissue. Naughton et al teach a method for treatment of ischemic tissue, particularly myocardial ischemia, by producing and implanting a three-dimensional stromal tissue construct to the ischemic region of the heart to promote vascularization of the heart and regeneration of the damaged cardiac muscle cells (which applicant calls organ augmentation) (See Naughton et al, Pg. 2, paragraph 0028). The method of Naughton et al comprises formation of a three-dimensional stromal tissue construct by inoculating stromal cells onto a three-dimensional scaffold; and then implantation of the three-dimensional tissue construct at various locations where the heart tissue was damaged by ischemia so as to allow assimilation of the stromal cells into the natural cardiac tissue (See Naughton et al, Pg. 5, paragraphs 0055-0057). It would further have been obvious to one of ordinary skill in the art, at the time the invention was made, to implant multiple tissue constructs at multiple sites, as needed to correct ischemic damage. One would be motivated to produce and implant as many tissue constructs as needed to correct all areas of ischemic damage in order to fully treat a patient.

Regarding the material of the three-dimensional scaffold (matrix), Naughton et al teach the three-dimensional scaffold can consist of PGA, collagen, polylactic acid (a polymer) or hyaluronic acid (See Naughton et al, Pg. 2, paragraph 0032). Though Naughton et al implant a three-dimensional 'organ

construct' into the target tissue area, at the time the invention was made it was well known that various substrate materials and forms could be successfully utilized for delivery of cells to a target tissue region for assimilation into the target tissue. In support, MacLaughlin et al and Atala et al are referenced. MacLaughlin et al discusses the three main types of matrices: microfabricated devices, fibrous scaffolds (such as that of Naughton et al), and injectable hydrogels; more specifically, with regards to hydrogels, MacLaughlin et al disclose various polymeric materials, including collagen, which are used as the injectable hydrogel materials (See MacLaughlin et al, abstract & col. 7-14). Similarly, Atala et al also disclose various matrix materials and forms which are commonly used in the field of tissue engineering and cell delivery, including hydrogels and decellularized tissue (See, e.g. Atala, Pg. 1, paragraph 0012). Therefore, at the time the invention was made different matrix material and forms were recognized as suitable for delivery of cells to the body for purposes of tissue engineering and augmentation of existing tissues within the body; thus, though Naughton et al utilize pre-formed scaffold frameworks, it would have been obvious to the skilled artisan to alternatively use alternative scaffold forms, including injectable polymeric hydrogels, including type I collagen, or decellularized tissue, as the matrix material for culture and delivery of the cells, and use of these various other forms would be expected to yield the same result (successful delivery of the cells to the target tissue site). Substitution of one element for another known in the field is considered to be obvious, absent a showing that the result of the substitution yields more than predictable results. See *KSR International Co. v Teleflex Inc* 82 USPQ2d 1385 (US 2007) at page 1395.

Regarding the types of cells cultured on the three-dimensional scaffold Naughton et al teach the stromal cell populations can comprise fibroblasts as well as tissue specific cells, such as heart cells, particularly cardiac muscle cells and aortic smooth muscle cells (See Naughton et al, Pg. 3, paragraph 0034 & claims 3 and 4). Additional cells can be added to form the three-dimensional tissue, including endothelial cells (See Naughton et al, Pg. 3, paragraph 0038). It would have been obvious to one of

ordinary skill in the art to additionally include endothelial cells, particularly vascular endothelial cells, in the three-dimensional tissue construct of Naughton et al because at the time the invention was made, inclusion of vascular endothelial cells, in addition to stromal/parenchymal cells, in tissue engineered constructs was known to promote formation of a primitive vascular system (See Atala, col. 2, ln 19-52). Thus, because one of the goals of the tissue construct of Naughton et al is to promote vascularization in the tissue construct, one would be motivated to include the vascular endothelial cells which were known to promote such vasculogenesis (See Naughton et al, Pg. 1, paragraph 0007). Thereby, upon implantation of the tissue construct, Naughton et al effectively co-administers both the stromal cells, which may comprise myoblasts and other tissue specific cells, as well as vascular endothelial cells.

Naughton et al does not teach a further step of implanting encapsulated cells which have been genetically engineered to express an angiogenesis modulating agent. However, methods of repairing ischemic tissue involving implantation of encapsulated cells which have been genetically engineered to express angiogenesis modulating agents, such as VEGF or FGF-2, so to improve survival and vascularization at the implantation site were taught by Springer et al and Rinsch et al:

Springer et al discloses a method wherein myoblasts transfected to express VEGF are encapsulated in alginate-PLL microcapsules and then injected either subcutaneously or into the peritoneal cavity to promote blood vessel formation (See Springer et al, Pg. 280, col. 2). Springer et al report that, unlike non-encapsulated cells (their previous work) the encapsulated cells led to blood vessel formation and recruitment of endothelial and smooth muscle cells (See Springer et al, pg. 286, col. 2 – Pg. 287, col. 1).

Rinsch et al disclose a method for promoting revascularization and healing of ischemic skin tissue. Their method involves implanting encapsulated, genetically engineered myoblasts, wherein the myoblasts were transfected with VEGF or FGF-2 (See Rinsch et al, Pg. 524, col. 1), under the ischemic

zone at the time of implantation of a transplanted skin flap. In tissues wherein cells expressing FGF-2 were implanted, Rinsch et al report decreased necrosis (See Rinsch et al, Pg. 526, Table 2). Rinsch et al report formation of blood vessels around the implanted capsules (see Rinsch et al, pg. 526, col. 2).

While both Springer et al and Rinsch et al report increased recruitment of endothelial cells and muscle cells and neo-blood vessel formation, both Springer et al and Rinsch et al also note that constituent expression of the angiogenesis modulating genes can produce deleterious results, so they suggest using transfection methods whereby the gene expression can be controlled (See Springer et al, Pg. 287, col. 1-2) or halting treatment after revascularization (See Rinsch et al, Pg. 524, col. 1). Following Springer et al's suggestion, it would have been obvious to one of ordinary skill in the art to use myoblasts which will transiently express the angiogenesis modulating gene(s); such methods were known in the art, see Penn et al.

Penn et al teach transfecting a population of skeletal myoblasts with a VEGF expression vector by plasmid DNA transfection (See Penn et al, Pg. 7, paragraph 0092). Penn et al also teach that the VEGF can be transiently expressed for any suitable and defined length of time (See Pg. 8, paragraph 0100-0102). Penn et al teach that local and transient expression of VEGF is sufficient to induce neovascularization and minimize systemic effects and hemangioma formation (See Penn et al, Pg. 1, paragraph 0004). With regards to the length of time the VEGF is produced, Penn et al teach that the duration of the transient expression is a result effective variable that would be routinely optimized by one of ordinary skill in the art (See Penn et al, pg. 8, paragraphs 0099-0102). Penn et al teach that the cells can be transiently transfected so as to express a therapeutic amount of VEGF; Penn et al further teaches that it is well within the scope of one skilled in the art to determine the appropriate therapeutic amount on an individual basis, as factors such as size, age, sex, presence of other drugs, and concentration of the active drug, all effect the optimal duration of expression. Therefore, the duration of the transient expression of VEGF would have been routinely optimized by one of ordinary skill in the art at the time

the invention was made, especially with lack of evidence to the contrary, submitting the claimed time period is critical. Penn et al further add that their cells, which transiently express VEGF, are useful to stimulate cell differentiation and regenerate ischemia damaged tissue (See Penn et al, Pg. 2, paragraph 0020 & Pg. 3, paragraphs 0044-0045). Therefore, at the time the invention was made, the benefits of transiently transfected cells, compared to constitutively transfected cells, was recognized in the art, and methods for producing such transiently transfected cells were known. Thus, in order to provide optimal and controlled delivery of the angiogenesis modulating agents, it would have been obvious to the artisan of ordinary skill to encapsulate transiently transfected cells in the methods of Springer et al and/or Rinsch et al.

Therefore, it is submitted that combining the therapies of implanting new engineered tissue to sites of ischemic tissue (disclosed by Naughton et al) and delivering microcapsules containing cells genetically engineered to transiently express angiogenesis modulating agents to sites of ischemic tissue (disclosed by Springer et al and Rinsch et al, taken in view of Penn et al) into a single method would have been obvious to one of ordinary skill in the art at the time the invention was made. Based on the recognized need to find an effective treatment for revascularizing ischemic tissue, one of ordinary skill in the art would have been motivated to try to combine known therapies to develop a more effective solution for the known problem, as a person with ordinary skill has good reason to pursue the known options within his or her technical grasp. See *KSR International Co v Teleflex Inc,* (cited *supra*) at page 1398. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Examiner, Art Unit 1651